COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study

Article (Accepted Version)

COVID-19 in children and adolescents in Europe – a multinational, multicentre cohort study

Florian Götzinger MD *[1], Begoña Santiago-Garcia MD PhD *[2], Antoni Noguera-Julian MD PhD [3,4,5,6], Miguel Lanaspa MD PhD [3], Laura Lancella MD [7], Francesca I Calò Carducci, MD PhD [7], Natalia Gabrovska MD [8], Svetlana Velizarova MD [8], Petra Prunk MD [9], Veronika Osterman MD [9], Uros Krivec MD [10], Andrea Lo Vecchio MD PhD [11], Delane Shingadia MD [12,13], Antoni Soriano Arandes MD PhD [14], Susana Melendo MD [14], Marcello Lanari MD PhD [15], Luca Pierantoni MD PhD [15], Noémie Wagner MD [16], Arnaud G. L'Huillier MD [16], Ulrich Heininger MD [17], Nicole Ritz MD PhD [17,18], Srini Bandi MD [19], Nina Krajcar MD [20], Srđan Roglić MD PhD [20], Mar Santos MD [2], Christelle Christiaens MD [21], Marine Creuven MD [21], Danilo Buonsenso MD [22], Steven B Welch FRCPCH [23], Matthias Bogyi MD [1], Folke Brinkmann MD [24], Marc Tebruegge MD PhD, [13,18,25]
on behalf of the ptbnet COVID-19 Study Group **

1. Department of Paediatric and Adolescent Medicine, National Reference Centre for Childhood Tuberculosis, Wilhelminenspital, Vienna, Austria.
2. Department of Paediatric Infectious Diseases, University Hospital Gregorio Marañón and Gregorio Marañón Research Institute (IiSGM), Madrid, Spain.
3. Malalties Infeccioses i Resposta Inflamatòria Sistèmica en Pediatria, Unitat d´Infeccions, Servei de Pediatria, Institut de Recerca Pediàtrica Hospital Sant Joan de Déu, Barcelona, Spain.
4. Departament de Pediatria, Universitat de Barcelona, Barcelona, Spain.
5. CIBER de Epidemiología y Salud Pública, CIBERESP, Madrid, Spain.
6. Red de Investigación Translacional en Infectología Pediátrica, RITIP, Madrid, Spain.
7. Academic Department of Paediatrics, Bambino Gesù Children's Hospital, Rome, Italy.
8. Children's Clinic, Department of Pulmonary Diseases, MHATLD "St. Sofia", Medical University Sofia, Sofia, Bulgaria.
9. Department of Infectious Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia.

10. Department of Paediatric Pulmonology, University Medical Centre Ljubljana, Ljubljana, Slovenia.
11. Section of Paediatrics, Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy.
12. Department of Paediatric Infectious Diseases, Great Ormond Street Hospital, London, UK.
13. Department of Infection, Immunity & Inflammation, UCL Great Ormond Street Institute of Child Health, University College London, London, UK.
14. Paediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Barcelona, Spain.
15. Medical and Surgical Science Department, S. Orsola University Hospital, Bologna, Italy.
16. Paediatric Infectious Diseases Unit, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.
17. Department of Paediatric Infectious Diseases and Vaccinology, University of Basel Children´s Hospital, Basel, Switzerland.
18. Department of Paediatrics, Royal Children's Hospital Melbourne, University of Melbourne, Melbourne, Australia.
19. Department of Paediatrics, Leicester Children's Hospital, Leicester, UK.
20. Department of Paediatric Infectious Diseases, University Hospital for Infectious Diseases, Zagreb, Croatia.
21. Department of Paediatric Infectious Diseases, CHC Montlegia, Liège, Belgium.
22. Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
23. Birmingham Chest Clinic and Heartlands Hospital, University Hospitals Birmingham, Birmingham, UK
24. Department of Paediatric Pulmonology, Ruhr University Bochum, Bochum, Germany.
25. Department of Paediatric Infectious Diseases & Immunology, Evelina London Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London, UK.

***** Drs. Florian Götzinger and Begoña Santiago-Garcia contributed equally to this study.

**** ptbnet COVID-19 Study Group**:

Jasmin Pfefferle and Angela Zacharasiewicz, Wilhelminenspital, Vienna, Austria; Angelika Berger, Medical University Vienna, Vienna, Austria; Roland Berger, St. Josef Hospital, Vienna, Austria; Volker Strenger and Daniela S. Kohlfürst, Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria; Anna Zschocke and Benoît Bernar, Department of Pediatrics, Medical University Innsbruck, Innsbruck, Austria; Burkhard Simma, Landeskrankenhaus Feldkirch, Feldkirch, Austria; Edda Haberlandt, Krankenhaus Dornbirn, Dornbirn, Austria; Christina Thir and Ariane Biebl, Kepler University Hospital, Linz, Austria; Koen Vanden Driessche and Tine Boiy, Antwerp University Hospital, Antwerp, Belgium; Daan Van Brusselen, GZA Hospitals Antwerp, Antwerp, Belgium; An Bael, ZNA Paola Children's Hospital Antwerp & University of Antwerp, Antwerp, Belgium; Sara Debulpaep and Petra Schelstraete, Gent University Hospital, Gent, Belgium; Ivan Pavić, Children's Hospital Zagreb, Zagreb, Croatia; Ulrikka Nygaard, Copenhagen University Hospital, Denmark; Jonathan Peter Glenthoej, Nordsjaellands Hospital, Hilleroed, Denmark; Lise Heilmann Jensen, Zealand University Hospital, Roskilde, Denmark; Ilona Lind, Pärnu Hospital, Pärnu, Estonia; Mihhail Tistsenko, West-Tallinn Central Hospital, Tallinn, Estonia; Ülle Uustalu, Tallinn Children's Hospital, Tallinn, Estonia; Laura Buchtala, Klinikum Bremen-Mitte, Bremen, Germany; Stephanie Thee, Charité Universitätsmedizin, Berlin, Germany; Robin Kobbe and Cornelius Rau, University Children's Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Nicolaus Schwerk, Hannover Medical School, Hannover, Germany; Michael Barker, Helios Klinikum Emil von Behring, Berlin, Germany; Maria Tsolia and Irini Eleftheriou, 2nd Dept of Pediatrics, National & Kapodistrian University of Athens, P. & A. Kyriakou Children's Hospital, Greece; Patrick Gavin and Oksana Kozdoba, Children's Health Ireland at Crumlin and Temple Street, Dublin, Ireland; Borbàla Zsigmond, Heim Pal Children's Hospital, Budapest, Hungary; Piero Valentini, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Inga Ivaškevičienė and Rimvydas Ivaškevičius, Clinic of Children's Diseases, Institute of Clinical Medicine, Vilnius University, Vilnius, Lithuania; Valentina Vilc, Institute of Phthisiopneumology, Chisinau, Moldova; Elisabeth Schölvinck, Beatrix Children's Hospital University Medical Centre Groningen, Groningen, The Netherlands; Astrid Rojahn, Oslo University Hospital, Oslo, Norway; Anastasios Smyrnaios, St. Olavs University Hospital, Trondheim,

Norway; Claus Klingenberg, University Hospital of North Norway, Tromso, Norway; Isabel Carvalho and Andreia Ribeiro, Hospital Center of Vila Nova de Gaia/Espinho, Porto, Portugal; Anna Starshinova, Almazov National Medical Research Centre, St. Petersburg, Russia; Ivan Solovic, National Institute for TB, Lung Diseases and Thoracic Surgery, Vysne Hagy, Slovakia; Lola Falcón and Olaf Neth, Hospital Infantil Virgen del Rocío, Sevilla, Spain; Mario Pérez-Butragueño, Hospital Universitario Infanta Leonor, Madrid, Spain; Laura Minguell, Hospital Universitari Arnau de Vilanova, Lleida, Spain; Matilde Bustillo and Aida María Gutiérrez-Sánchez, Miguel Servet University Hospital, Zaragoza, Spain; Borja Guarch Ibáñez, Hospital Universitari de Girona Dr. Josep Trueta, Girona, Spain; Francesc Ripoll, Hospital Santa Caterina, Girona, Spain; Beatriz Soto, Hospital Universitario de Getafe, Madrid, Spain; Karsten Kötz, Queen Silvia Children's Hospital, Gothenburg, Sweden; Petra Zimmermann, Hôpital Fribourgeois, Fribourg, Switzerland; Hanna Schmid, University Children's Hospital Basel, Basel, Switzerland; Franziska Zucol, Kantonsspital Winterthur, Winterthur, Switzerland; Anita Niederer, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland; Michael Buettcher, Lucerne Children's Hospital, Lucerne Cantonal Hospital, Lucerne, Switzerland; Benhur Sirvan Cetin, Erciyes University Hospital, Kayseri, Turkey; Olga Bilogortseva, National institute of Phthisiology and Pulmonology, Kiev, Ukraine; Vera Chechenyeva, National Specialised Children's Centre for HIV & AIDS, Kiev, Ukraine; Alicia Demirjian, Evelina London Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London, UK; Fiona Shackley, Sheffield Children's Hospital, UK; Lynne McFetridge, Antrim Area Hospital, Antrim, UK; Lynne Speirs, Royal Belfast Hospital for Sick Children, Belfast, UK; Conor Doherty, Royal Hospital for Children, Glasgow, UK; Laura Jones, Royal Hospital for Sick Children, Edinburgh, UK; Paddy McMaster, North Manchester Care Organisation, Manchester, UK; Clare Murray and Frances Child, Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, UK; Yvonne Beuvink and Nick Makwana, City and Sandwell Hospitals Birmingham, Birmingham, UK; Elisabeth Whittaker, St. Mary's Hospital Paddington, London, UK; Amanda Williams, London North West University Healthcare NHS Trust, Harrow, UK; Katy Fidler, Royal Alexandra Children's Hospital, Brighton, UK; Jolanta Bernatoniene, Bristol Royal Hospital for Children, Bristol, UK; Rinn Song and Zoe Oliver, Oxford Children's Hospital, Oxford, UK; Andrew Riordan, Alder Hey Children's Hospital, Liverpool, UK.

Corresponding author:
Dr Marc Tebruegge, Department of Infection, Immunity and Inflammation,
UCL Great Ormond Street Institute of Child Health, University College London
30 Guildford Street, London WC1N 1EH, United Kingdom.
Email: m.tebruegge@ucl.ac.uk

Key words: coronavirus, SARS-CoV-2, child, treatment, intensive care

Running title: COVID-19 in children in Europe

ABSTRACT

Background

To date the published data on COVID-19 in children remain very limited, and most reports originate from China. This study aimed to capture key data on children with SARS-CoV-2 infection across Europe to inform physicians and healthcare service planning during the ongoing pandemic.

Methods

Multicentre study involving 82 participating healthcare institutions across 25 European countries, using a well-established research network – the Paediatric Tuberculosis Network European Trials Group (ptbnet) – mainly comprising Paediatric Infectious Diseases specialists and Paediatric Pulmonologists, over a 3·5-week period in April 2020, at the initial peak of the European COVID-19 pandemic. Inclusion criteria comprised: age ≤18 years and SARS-CoV-2 detected at any anatomical site.

Findings

A total of 582 PCR-confirmed cases were included [median age: 5·0 years (IQR: 0·5-12·0); male to female ratio 1·15:1]. One-hundred forty-five (24·9%) had significant pre-existing medical conditions. The majority (n=363; 62·4%) were admitted to hospital. Forty-eight (8·2%) required intensive care unit (ICU) support, 25 (4·3%) mechanical ventilation (median duration: 7 days; range: 1-34 days), 19 (3·3%) inotropic support, and one (0·1%) extracorporeal membrane oxygenation. Significant risk factors for requiring ICU support in multivariate analyses were age <1 month, male gender, pre-existing medical condition, and presence of lower respiratory tract infection symptoms at presentation. The most frequently used drug with antiviral activity was hydroxychloroquine, followed by remdesivir, lopinavir/ritonavir and oseltamivir. Immunomodulatory medication used included corticosteroids, intravenous immunoglobulin, tocilizumab, anakinra and siltuximab. Four children died (case fatality rate: 0·69%; 95%CI: 0·20-1·82%); the remaining 578 survived without apparent sequelae.

Interpretation

COVID-19 is generally a mild disease in children, including infants. However, a small proportion develop severe disease requiring ICU support and prolonged ventilation, although fatal outcome is overall rare. The data also reflect the current uncertainties regarding specific treatment options, highlighting that additional data on antiviral and immunomodulatory drugs are urgently needed.

Funding

ptbnet is supported by Deutsche Gesellschaft für Internationale Zusammenarbeit.

Evidence before this study

We conducted a Medline search through the PubMed interface to identify publications describing clinical studies in children with COVID-19 on the 7th of May 2020. To make the search broad, the search terms used were: (child OR children OR pediatric OR paediatric) AND COVID-19; no additional limits were set. This yielded a total of 809 papers: 332 were unrelated to children with COVID-19; 104 case reports or case series; 38 epidemiological reports; 66 guidelines and consensus statements; 184 reviews, perspectives, or editorials without original data; and 53 letters. Twenty-two papers presented original data, but exclusively in adults. Only 10 papers reported clinical studies in children with COVID-19: eight papers originated from China, one from Spain and one from Italy. The study by Tagarro *et al.* was reported in letter format, and only included 41 children with confirmed SARS-CoV-2 infection in Madrid. The study from Italy by Parri *et al.* was also reported as a letter and included 100 cases across several Italian hospitals. However, the study only featured a single patient who required mechanical ventilation, and consequently very little data on children with COVID-19 at the severe end of the disease spectrum.

Added value of the study

This study is the first multinational, multicentre study in children with COVID-19, and provides a detailed overview on SARS-CoV-2 infection in children in Europe during the initial peak of the pandemic, which was facilitated by a collaboration of 82 units across 25 European countries. The study has several key findings. Firstly, the data show that COVID-19 is generally a mild disease in children, including infants. Secondly, the study found that a significant proportion of children develop severe disease, requiring intensive care support and prolonged ventilation. Several predisposing factors for requiring intensive care support were identified. Thirdly, the study confirms that fatal outcome is rare in children. There was considerable variability in the use of drugs with antiviral activity as well as immunomodulatory medication, reflecting current uncertainties regarding specific treatment options.

Implications of all the available evidence

This study confirms previous reports from China suggesting that the case fatality rate of COVID-19 in children is substantially lower than in elderly patients. However, some children develop severe disease and require prolonged intensive care support,

which should be accounted for in the planning of healthcare services and allocation of resources during the ongoing pandemic. Finally, the findings highlight that data on antiviral and immunomodulatory drugs are urgently needed from well-designed, randomised controlled trials in children, to enable paediatricians to make evidence-based decision regarding treatment choices for children with severe COVID-19.

Introduction

In late December 2019, the World Health Organization was notified of an unusual cluster of pneumonia cases in Wuhan, China. The disease, later termed coronavirus disease 2019 (COVID-19), spread quickly beyond the borders of China, with the first cases in Europe being recorded on 25 January 2020.[1]

Subsequent investigations identified a novel betacoronavirus now designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Currently there are no antiviral treatment options with proven efficacy, but several randomized controlled trials (RCTs) are currently investigating a number of agents, including hydroxychloroquine, lopinavir/ritonavir, favipiravir and remdesivir (e.g. NCT04336904, NCT04328285 and NCT04280705). Other trials are focusing on immunomodulators, including tocilizumab and anakinra (e.g. NCT04317092 and NCT04330638).

To date, the available data on COVID-19 in children and adolescents remain very limited, despite the number of confirmed COVID-19 cases now exceeding five million globally.[3,4] Most published data originate from China, which cannot necessarily be extrapolated to children in Europe and elsewhere.[5-12] Also, existing papers from China contain very few clinical data on children, and most lack details regarding supportive measures required by children with COVID-19. Similarly, recent epidemiological reports from Europe and North America contain limited clinically relevant information.[13,14] Determining the level of support required by children is essential for paediatric service planning during the ongoing COVID-19 pandemic.

By use of a well-established research network, predominately comprising Paediatric Infectious Diseases specialists and Paediatric Pulmonologists, the aim of this study was to rapidly capture key data on COVID-19 in children in Europe on a large scale, to aid physicians in Europe and in other geographical locations with service planning and allocation of resources.

Methods

European members of the Paediatric Tuberculosis Network European Trials Group (ptbnet), which currently includes 304 clinicians and researchers, most of whom are based at tertiary/quaternary Paediatric Infectious Diseases or Paediatric Pulmonology units, across 128 paediatric healthcare institutions in 31 European countries,[15-20] were invited to contribute confirmed COVID-19 cases that had been managed at or managed remotely by their healthcare institution (including cases admitted to other hospitals and cases identified during community screening). A standardized data collection spreadsheet was used by collaborators to record the data from their centre. All data were reviewed by three of the investigators (FG, BSG, and MT), and any inconsistencies and other data queries were clarified with the reporting collaborator(s). Units that did not see any cases prior to or during the study period were asked to report the absence of cases fulfilling the inclusion criteria at the end of the study period. The study was conducted over a 3·5-week period, from April 1 to April 24, 2020.

Study definitions

A confirmed COVID-19 case was defined as a patient in whom SARS-CoV-2 was detected in any clinical sample (respiratory tract, blood, stool or cerebrospinal fluid) by reverse transcriptase polymerase chain reaction (RT-PCR). PCR testing was performed as part of routine clinical care, and therefore done according to local testing guidelines in place at the time. The upper age-limit for inclusion was 18 years. Date of symptom onset was defined as the day when the first symptom or sign occurred, and date of diagnosis as the day when SARS-CoV-2 was first detected. Pyrexia was defined as a body temperature ≥38·0ºC. Index case was defined as the most likely source case based on history; if multiple family members were affected, the person who displayed symptoms first was recorded. The diagnosis of upper respiratory tract infection (URTI) was based on clinical symptoms, encompassing any of the following: coryza, pharyngitis, tonsillitis, otitis media, sinusitis. Lower respiratory tract infection (LRTI) was based on clinical signs and auscultation findings. Inotropic support was defined as administration of dopamine, dobutamine, adrenaline or noradrenaline by continuous infusion.

Statistical methods

Non-parametric two-tailed Mann Whitney *U* tests were used to compare continuous variables, and chi-square or Fisher's exact tests for categorical variables, as appropriate. The 95% confidence interval (95%CI) around the case fatality rate was calculated with the Wald method. Normality of data distribution was assessed with the Shapiro-Wilk test. The clinical end point was the need for admission to an intensive care unit [(ICU); either neonatal or paediatric intensive care]. Multivariable logistic regression analysis was performed with backward stepwise analysis exploring the variables significantly associated with ICU admission in univariate analysis. Factors associated with drug treatment were also explored. All probabilities are two-tailed. P-values <0·05 were considered statistically significant. All analyses were done with Prism (V8·0; GraphPad, La Jolla, U.S.) and SPSS (V25·0, IBM, Armonk, U.S.).

Ethical approvals

The study was reviewed and approved by the ptbnet steering committee, and the human research ethics committees of the University of Bochum, Germany (19-6545-BR), the Hospital Gregorio Marañon, Spain (CEIM HGUGM-177/20) and the city of Vienna, Austria (EK 20-071-VK). The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. No personal or identifiable data were collected during the conduct of this study.

Role of the funding sources

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all of the data and had the final responsibility to submit for publication.

Results

In total, 585 cases were reported from 77 healthcare institutions located in 21 European countries, including Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and United Kingdom (**Figure 1**). Three cases did not meet the inclusion criteria (one 21-year-old; two diagnosed with COVID-19 based on serological testing, but PCR-negative). Participating units (n=5) in The Netherlands, Moldova, Ukraine, and Russia, reported not having encountered any cases.

A total of 582 PCR-confirmed COVID-19 cases were included in the final analyses. The majority (n=454; 78·0%) were contributed by tertiary/quaternary healthcare institutions; fewer had been diagnosed in secondary (n=54; 9·3%) or primary healthcare (n=74; 12·7%) settings.

The median age of the study population was 5·0 years (range: 3 days-18 years; **Table 1**). Age was non-normally distributed (W=0·8710; p<0·0001), with more than a quarter (n=170; 29·2%) of cases aged <12 months (**Figure 2**). The male to female ratio was 1·15:1. The most common source of infection was a parent, considered the index case in 324 (55·6%) children; in 24 (4·1%) the likely index case was a sibling. In the remaining 234 (40·2%) children the index case was a person outside the immediate family or unknown. The majority of children (n=363; 62·4%) were admitted to hospital; 48 (8·2%) required admission to an ICU for additional support (corresponding to 13·2% of children admitted to hospital).

Pre-existing medical conditions and medication

Overall 437 (75·1%) cases had no pre-existing medical conditions. The remaining 145 (24·9%) children had significant medical conditions, most commonly chronic pulmonary disease (n=29, 5·0%; asthma: n=16; bronchopulmonary dysplasia: n=6), followed by malignancy (n=27, 4·6%; leukaemia/lymphoma: n=14; solid tumours: n=11), neurological conditions (n=26, 4·5%; epilepsy: n=9; cerebral palsy: n=8), congenital heart disease (n=25, 4·3%), chromosomal abnormalities (n=10, 1·7%; trisomy 21: n=8), and chronic renal disease (n=9, 1·5%). Seventeen patients had two or more pre-existing medical conditions.

Twenty-nine (5·0%) patients were receiving immunosuppressive medication at the time of COVID-19 diagnosis. Three (0·5%) had a previously diagnosed immunodeficiency, comprising common variable immunodeficiency, congenital neutropenia and Schimke immuno-osseous dysplasia. Twenty-five (4·3%) cases were receiving chemotherapy at the time of their diagnosis or had received chemotherapy in the preceding 6 months. Three (0·5%) had previously undergone human stem cell transplant.

Signs and symptoms

Pyrexia was common, observed in 379 (65·1%) cases. Approximately half had symptoms or signs of URTI and approximately one quarter had evidence of LRTI (**Table 1**); 128 (22·0%) had gastrointestinal symptoms. Forty (6·9%) patients with gastrointestinal symptoms had no respiratory symptoms; the majority of these patients had pyrexia (n=26; 65·0%). Ninety-two (16·0%) children were asymptomatic.

Symptom onset and time of diagnosis

The dates when SARS-CoV-2 infection was confirmed by RT-PCR in the study population are summarized in **Figure 3**. The median interval between symptom onset and diagnosis was 2 days (IQR: 1-4 days; range: 0-23 days); in the majority (n=391; 67·2%) of cases the interval was ≤3 days. In eight cases SARS-CoV-2 infection was confirmed before any signs or symptoms were present, mainly neonates born to SARS-CoV-2-positive mothers and household members of known, symptomatic COVID-19 cases.

Radiological findings and additional virological investigations

A chest radiograph was performed in 198 (34·0%) patients. Of those, 93 (47·0%) had changes consistent with pneumonia. Ten (5·1%) had changes suggestive of acute respiratory distress syndrome (ARDS), and all these patients required mechanical ventilation. In 29 (5%) cases additional viruses were detected in respiratory samples, comprising entero-/rhinovirus (n=18), influenza virus (n=5), parainfluenza virus (n=3), adenovirus (n=3), respiratory syncytial virus (RSV; n=2), bocavirus (n=2), coronavirus NL63, coronavirus HKU1, coronavirus OC43, and human metapneumovirus (n=1, each); in six cases two and in one three viruses were detected

simultaneously. Children with dual viral infection were more likely to have URTI or LRTI symptoms at presentation compared to those in whom no additional viral agent was identified (**Supplementary Appendix Table S1**). Furthermore, children with dual viral infection were significantly more likely to require ICU admission, respiratory support or inotropic support.

Respiratory and circulatory support

A total of 507 (87·1%) patients did not require respiratory support at any stage. Of the remaining 75 (12·9%) patients who required oxygen support, 31 (5·3%) were started on continuous positive airway pressure (CPAP) and 25 (4·3%) on mechanical ventilation (including 14 that had been managed with CPAP initially). The median duration of mechanical ventilation was 7 days (IQR: 2·3-10·8 days; range: 1-34 days). One patient was started on extracorporeal membrane oxygenation. Nineteen (3·3%) cases required support with inotropes.

Comparison of children managed with and without intensive care support

A comparison of cases requiring ICU support and those who did not (i.e. children in the community and those admitted to hospital, but not needing ICU support) is shown in **Table 1**. Overall, the median age of the former group was lower (median age 4·0 vs. 5·5 years; **Figure 2**), but this was not statistically significant. In univariable analysis, age <1 month, male gender, pre-existing medical condition, pyrexia, LRTI symptoms, radiological changes suggestive of pneumonia or ARDS, and dual viral infection were associated with ICU admission (**Table 1**). In multivariable analysis, the factors that were associated with ICU admission were: age <1 month (odds ratio (OR): 5·06; 95%CI: 1·72-14·87; p=0·003), male gender (OR: 2·12; 95%CI: 1·06-4·21; p=0·033), LRTI symptoms (OR: 10·46; 95%CI: 5·16-21·23; p=<0·0001), and pre-existing medical condition (OR: 3·27; 95%CI: 1·67-6·42; p=0·001).

Antiviral and immunomodulatory treatment

The most commonly used drug with antiviral activity was hydroxychloroquine, used in 40 patients, followed by remdesivir used in 17. Lopinavir/ritonavir was used in six patients and oseltamivir in three (n=2 had influenza virus co-infection). Three patients received two drugs with antiviral activity, and one three; all four had ARDS on chest radiography. No patient received chloroquine, favipiravir, zanamivir or ribavirin.

With regard to immunomodulatory medication, 22 patients received systemic corticosteroids, seven intravenous immunoglobulin, four tocilizumab, three anakinra, and one siltuximab. Factors associated with treatment initiation of drugs with antiviral and/or immunomodulatory activity comprised: pre-existing malignancy, cardiac or respiratory disease; immunosuppressive therapy at presentation or recent chemotherapy; radiological findings suggestive of pneumonia or ARDS; and dual viral infection (**Supplementary Appendix Table S2**).

Final outcome

Four patients, all >10 years-of-age, had a fatal outcome [case fatality rate (CFR): 0·69%; 95%CI: 0·20-1·82%], with death occurring at 3, 9, 11 and 17 days after symptom onset. Two patients had no known pre-existing medical conditions; one had a cardio-respiratory arrest prior to arrival in the hospital and resuscitation was unsuccessful; the other died while being mechanically ventilated in ICU. Another patient had undergone human stem cell transplant fifteen months earlier. One patient was managed palliatively (without intubation), due to the severity of the pre-existing medical conditions. The remaining 578 patients were alive when the study closed. Ninety-three (16·1%) patients never developed clinical symptoms. In 460 (79·6%) patients all symptoms had resolved without apparent sequelae, while 25 (4·3%) were still symptomatic and/or requiring respiratory support when the study closed.

Discussion

To our knowledge this is the first multi-national, multicentre study on paediatric COVID-19, and also the largest clinical study in children outside China to date. The inclusion of such a substantial number of cases was made possible by involving a large number of specialist centres across Europe via a well-established collaborative paediatric TB research network, allowing this study to provide one of the most detailed accounts of COVID-19 in children published to date.

It is important to highlight that this study has primarily captured data from children who were seen or managed within the hospital setting, and that the majority of participating units were part of tertiary/quaternary healthcare institutions. Consequently the study population is likely to primarily represent children at the more severe end of the disease spectrum. Notably, a recent letter summarizing 171 PCR-confirmed cases in Wuhan suggests that close to 20% of children with SARS-CoV-2 infection are asymptomatic.[10] At the time our study was conducted, testing capacity for SARS-CoV-2 in many European countries was lower than clinical demand, and therefore many children with symptoms consistent with COVID-19 in the community were not tested and consequently not diagnosed. Nevertheless, our data indicate that children are overall less severely affected by COVID-19 than adults, particularly elderly patients. Previous, large-scale data suggest that the CFR in adults >70 years is close to 10%,[6] potentially due to immunosenescence.[21] It is reassuring that our data show that severe COVID-19 is uncommon in young children, including infants, despite their immune maturation being incomplete,[22,23] with only few requiring mechanical ventilation. Strikingly, all children who died in our cohort were older than 10 years.

A recent publication from the Centers for Disease Control and Prevention (CDC), summarizing epidemiological data from the United States, reported that there were a total of 2,572 confirmed COVID-19 cases aged <18 years as of the April 2, 2020, representing only 1·7% of the total number of recorded cases (n=149,760).[14] A recent paper from the Australian Health Protection Agency also reported that children accounted for only 4% of the confirmed COVID-19 cases in Australia.[24] Unfortunately, in the U.S. report clinical data were only available in a small

proportion of patients (n=291; 11%). In concordance with our observations, fever and cough were the predominant clinical features at presentation (present in 56% and 54% of cases, respectively), with similar rates also observed in a study from Italy.[25] In our cohort almost a quarter of patients had gastrointestinal symptoms, some of whom had no respiratory symptoms, and a substantial proportion of children were entirely asymptomatic.

The CDC report also mentions three deaths, but it is unclear how many patients were still hospitalized by the time of publication, so it is difficult to come to firm conclusions regarding the CFR in U.S. children.[14] Our data indicate that the CFR in children across Europe is below one percent. Considering that many children with mild disease will never have been brought to medical attention, and therefore not diagnosed, it is highly probable that the true CFR is substantially lower than the figure of 0·69% observed in our cohort. This hypothesis is further supported by an epidemiological study from China, in which the CFR in individuals ≤19 years was only 0·1% (1 death in 965 confirmed cases).[6] Furthermore, our data indicate that sequelae related to COVID-19 are likely to be rare in children. However, after the closure of our study reports of a hyperinflammatory syndrome affecting children that is temporally, and potentially causally, associated with SARS-CoV-2 infection have emerged, which has subsequently been named Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[26,27] Further research will be required to characterise this emerging disease entity in detail, and determine the long-term outcome of affected children.

Importantly, our data show that severe COVID-19 can occur both in young children and in adolescents, and that a significant proportion of those patients require ICU support, frequently including mechanical ventilation. A small, recently published study from Madrid also found that 4 (9·7%) out of 41 children with SARS-CoV-2 infection required admission to ICU.[28] In our cohort, age <1 month, male gender, presence of LRTI symptoms at presentation, and presence of a pre-existing medical condition were associated with a increased likelihood of requiring ICU support. Our results also show that the majority of children who are intubated due to respiratory failure require prolonged ventilation, often for one week or more. This contrasts with observations in children with RSV infection who on average only require mechanical

ventilation for five to seven days,[29] but is not dissimilar to observations in children with influenza.[30] This has important implications for service planning, as although the overall demand for ICU support may be lower in children than in adults, each patient is likely to occupy ICU space for an extended period of time. At this time of intense strain on healthcare services worldwide, it is vital that adequate resources are allocated to paediatric services in order to sustain the provision of high-quality care for children.

The observation that in our study children with dual viral infection (i.e. infected with SARS-CoV-2 and another viral agent) were more likely to require ICU support than those in whom SARS-CoV-2 was the only viral agent identified, may have implications for the winter period 2020/2021, when the incidence of other viral respiratory tract infections, including RSV and influenza virus infections, is bound to increase. This may result in a greater proportion of paediatric patients with COVID-19 requiring ICU support than in the cohort described here, as the influenza season 2019/2020 was already over in Europe before the study commenced (see https://flunewseurope.org/).

Our data also reflect the uncertainties regarding drug treatment options for COVID-19. In some countries, including Spain and Italy, national guidelines encourage the use of hydroxychloroquine for selected cases, as reflected in our data, while in other countries' recommendations are more guarded regarding the use of antiviral agents in the absence of robust human data. A recently published expert consensus statement from the U.S. emphasized that antiviral treatment should be reserved for patients at the severe end of the disease spectrum, ideally within a clinical trial.[31] Overall the expert panel appeared to favour the use of remdesivir over other agents, based on the currently available data from in vitro and animal studies, including in non-human primates, and recent data from compassionate use in humans.[32,33] The panel members' opinion was split regarding the use of lopinavir/ritonavir, given the disappointing results of a recently published RCT.[34]

The main limitation of this study relates to the limited number of variables collected. In the context of the ongoing COVID-19 pandemic, to ensure high levels of participation and avoid diverting substantial time away from clinical frontline duties,

a decision was made not to collect detailed data on laboratory parameters or ICU interventions. A further limitation was that a variety of in-house and commercial PCR assays were used across different participating centres, precluding any meaningful assessment of diagnostic test performance. Also, the number of children receiving antiviral or immunomodulatory treatment was too small to draw meaningful conclusions regarding their effectiveness, which will be addressed by the aforementioned RCTs. A further limitation is that different countries were using different thresholds to screen for SARS-CoV-2 at the time the study was performed, with some recommending screening of all children admitted to hospital and/or conducting community screening, whilst others were using more selective testing strategies. Despite those limitations, this study provides the most comprehensive overview on COVID-19 in children and adolescents to date.

In conclusion, our data, originating from a large number of specialist centres across Europe, show that COVID-19 is usually a mild disease in children, including infants. Nevertheless, a small proportion of children and adolescents develop severe disease and require ICU support, frequently needing prolonged ventilatory support. However, fatal outcome is rare overall. Our data also reflect the current uncertainties regarding specific treatment options, highlighting that more robust data on antiviral and immunomodulatory drugs are urgently needed.

Funding information: This project did not receive specific funding. ptbnet is supported by the Deutsche Gesellschaft für Internationale Zusammenarbeit. BSG is funded by the Spanish Ministry of Health - Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union (FEDER) [Contrato Juan Rodés, Grant JR16/00036]. ANJ was supported by "Subvencions per a la Intensificacio de Facultatius Especialistes" - Departament de Salut de la Generalitat de Catalunya, Programa PERIS 2016-2020 (SLT008/18/00193).

Contributor statement: MT conceived of the study. FG, BSG, SBW, MB, FB and MT designed the study. FG, BSG and MT cleaned and analysed the data, constructed the figures, and wrote the first draft of the manuscript. All authors contributed data to the study, contributed to the data interpretation, critically reviewed the manuscript, and approved the final manuscript for submission.

Potential conflicts of interest: FG has received funding from Gilead for research related to hepatitis E. BSG and MT have received assays free of charge from Cepheid for TB diagnostics projects. MT has received assays at reduced pricing or free of charge from Cellestis/Qiagen for TB diagnostics projects, has received support for conference attendance from Cepheid, and is currently receiving funding from bioMérieux as an investigator of an ongoing TB diagnostics study. The other authors declared no conflicts of interest.

Acknowledgements: The study team would like to express their gratitude to all colleagues and research personnel involved in the data collection for this study, as well as the members of the human research ethics committees and institutional review boards that have kindly fast-tracked this study. The authors are also grateful for the kind support of the Clinical Microbiology & Infectious Diseases Department and the COVID-19 Group at Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Table 1. Baseline demographic data, pre-existing medical conditions, concomitant medication, clinical features and radiological findings at presentation in the entire cohort, and comparisons between patients requiring intensive care unit (ICU) support and those who did not. Figures shown are numbers and percentages; p-values shown are based on univariable analyses. Odds ratios refer to the likelihood of admission to ICU.

	Entire cohort (n=582)	Not ICU (n=534)	ICU (n=48)	p-value	Odds ratio (95%CI)
Age median (IQR), years	5 (0·5 – 12·0)	5·5 (0·6 – 12·0)	4·0 (0·3 – 11·0)	0·20	0·9 (0·9 – 1·0)
<2 years	230 (39·5)	207 (38·8)	23 (47·9)		1·4 (0·8 – 2·6)
2-5 years	62 (10·7)	60 (11·2)	2 (4·2)		0·3 (0·1 – 1·4)
5-10 years	94 (16·2)	86 (16·1)	8 (16·7)		1·0 (0·4 – 2·3)
>10 years	196 (33·7)	181 (33·9)	15 (31·3)		0·8 (0·4 – 1·6)
Age <1 month	40 (6·9)	33 (6·2)	7 (14·6)	0·02	2·5 (1·0 – 6·2)
Gender (male)	311 (53·4)	278 (52·1)	33 (68·8)	0·02	2·2 (1·0 – 3·8)
Pre-existing medical conditions					
Any	145 (24·9)	120 (22·5)	25 (52·1)	<0·0001	3·7 (2·0 – 6·8)
Malignancy	27 (4·6)	22 (4·1)	5 (10·4)	0·04	2·7 (0·9 – 7·5)
Cardiac disease	25 (4·3)	20 (3·7)	5 (10·4)	0·02	2·9 (1·0 – 8·4)
Respiratory disease	29 (5·0)	23 (4·3)	6 (12·5)	0·01	3·1 (1·2 – 8·2)
Neurological disease	26 (4·5)	21 (3·9)	5 (10·4)	0·03	2·8 (1·0 – 7·9)
Renal disease	9 (1·5)	7 (1·3)	2 (4·2)	0·16	3·2 (0·6 – 16·2)
Chromosomal abnormality	10 (1·7)	8 (1·5)	2 (4·2)	0·19	2·8 (0·5 – 13·8)
Other	35 (6·0)	29 (5·4)	6 (12·5)	0·04	2·4 (0·9 – 6·3)
Immunosuppressive therapy *	29 (5·0)	26 (4·9)	3 (6·3)	0·72	1·3 (0·3 – 4·4)
Known Immunodeficiency	3 (0·5)	3 (0·6)	0 (0)	1·00	- **
Chemotherapy in last 6 months	25 (4·3)	23 (4·3)	2 (4·2)	1·00	0·9 (0·2 – 4·2)
Signs and symptoms ***					
Asymptomatic	92 (15·8)	90 (16·9)	2 (4·2)	0·02	0·2 (0·05 – 0·9)
Pyrexia	379 (65·1)	339 (63·5)	40 (83·3)	0·006	2·8 (1·3 – 6·2)
URTI	313 (53·8)	288 (53·9)	25 (52·1)	0·80	0·9 (0·5 – 1·6)
LRTI	143 (24·6)	108 (20·2)	35 (72·9)	<0·0001	10·6 (5·4 – 20·7)
Gastrointestinal	128 (22·0)	113 (21·2)	15 (31·3)	0·10	1·6 (0·8 – 3·2)
Headache ****	70 (27·5)	64 (27·1)	6 (31·6)	0·67	1·2 (0·4 – 3·4)
Radiological findings *****					
Suggestive of pneumonia	93 (47)	65 (41·7)	28 (66·7)	0·004	2·8 (1·3 – 5·7)
Suggestive of ARDS	10 (5·1)	0 (0)	10 (23·8)	<0·0001	- **
Dual viral infection	31 (5·3)	24 (4·5)	7 (14·6)	0·003	3·6 (1·4 – 8·9)

*At diagnosis of COVID-19.
** Odds ratio not calculated as one of the required values is zero.
*** Signs and symptoms at initial presentation.
**** Data on presence of headache only includes children ≥5 years of age in whom those data were recorded (n=255).
***** Chest radiograph performed in n=198 only (children without ICU admission, n=156; children with ICU admission, n=42).
Abbreviations: ARDS: acute respiratory distress syndrome, IQR: interquartile range, LRTI: lower respiratory tract infection, URTI: upper respiratory tract infection

Figure 1. Map showing the countries with participating units (n=81; unit locations indicated by blue dots), with shading indicating the number of cases contributed from each country. Countries highlighted in green had participating units that reported not having encountered any cases by study closure. Cities with more than one participating unit are represented by a single dot only (London n=4; Antwerp n=3; Madrid n=3; Vienna n=3; Barcelona n=2; Berlin n=2; Girona n=2, Manchester n=2; Rome n=2; Tallinn n=2; Zagreb n=2).

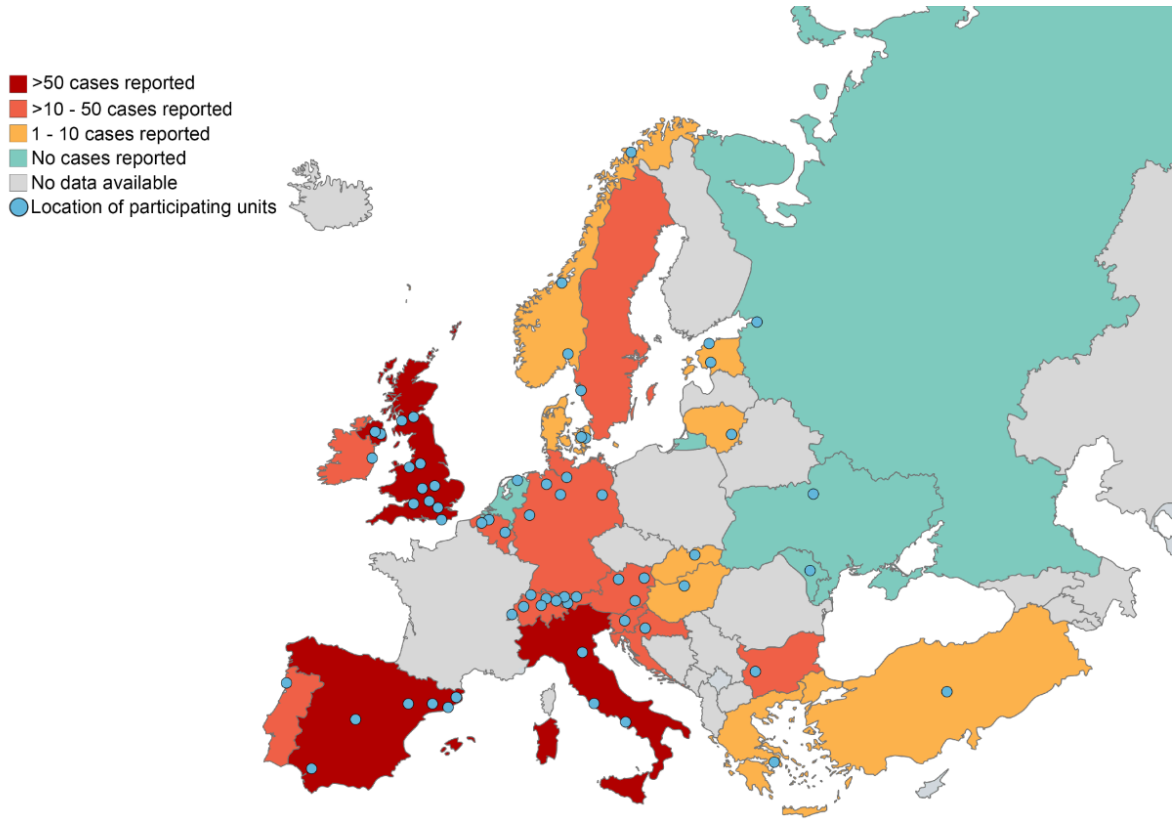


Figure 2. Violin plots showing the age distribution of patients who required intensive care support compared to those who did not. The solid lines represent the medians, the dashed lines the interquartile ranges.

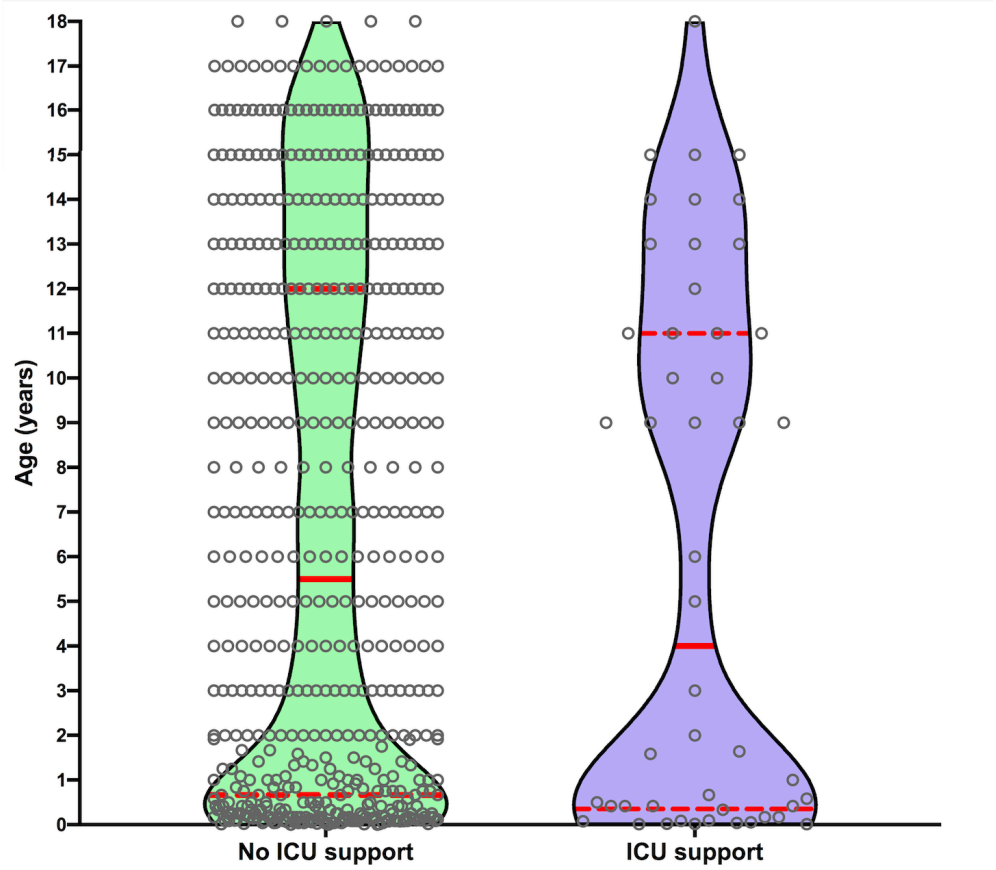
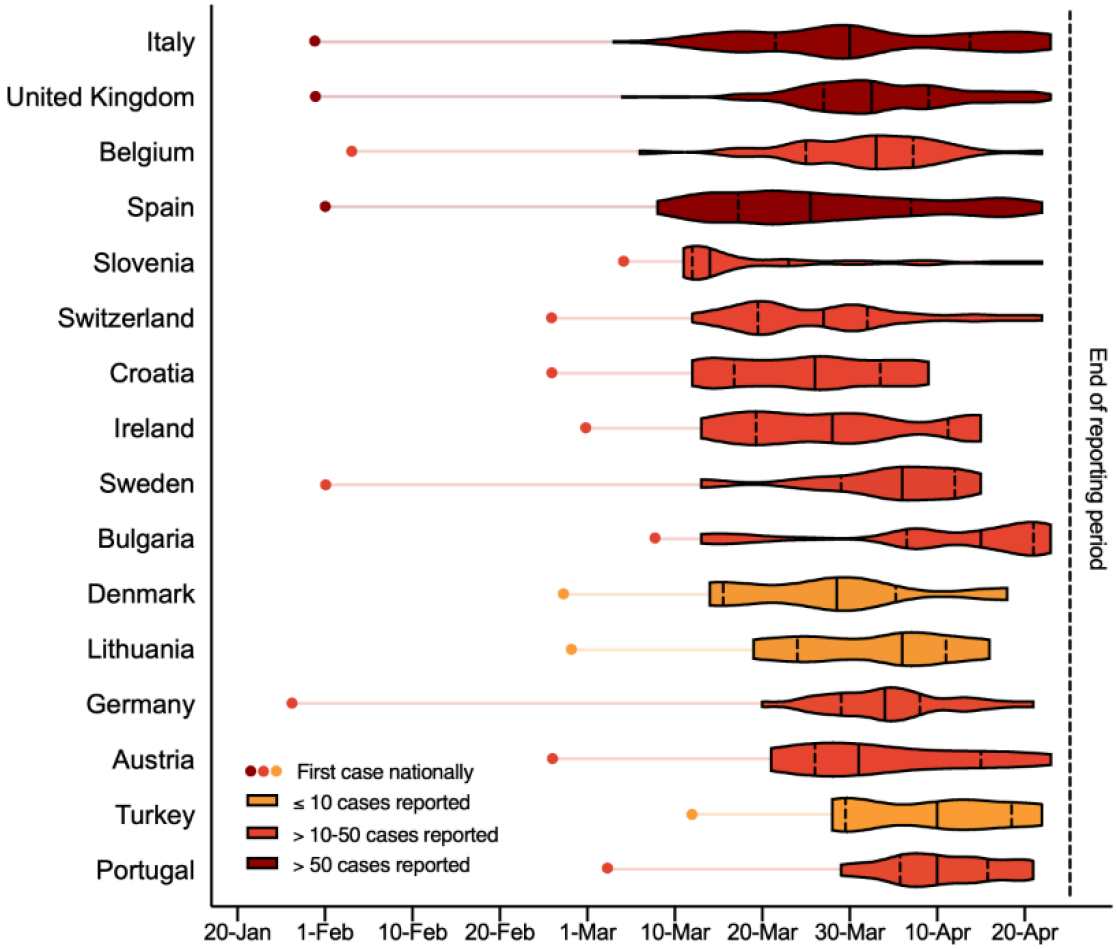


Figure 3. Violin plot illustrating the dates SARS-CoV-2 infection was confirmed by polymerase chain reaction in the study population, according to the country the cases were reported from. Countries with fewer than five cases reported are not shown. The shading reflects the number of cases contributed from each country. The lines represent the medians and the interquartile ranges. The date of the first case in each country is based on data reported by the European Centre for Disease Prevention and Control (https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html).



References

1. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 5. Available at: https://wwwwhoint/docs/default-source/coronaviruse/situation-reports/20200125-sitrep-5-2019-ncovpdf?sfvrsn=429b143d_8. Accessed 25 May 2020.
2. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020; **5**: 536-44.
3. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 126. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200525-covid-19-sitrep-126.pdf?sfvrsn=887dbd66_2. Accessed 25 May 2020.
4. Zimmermann P, Goetzinger F, Ritz N. Severe and fatal COVID-19 occurs in young children. *JAMA Pediatrics* 2020 (in press - DOI pending).
5. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* 2020; **26**: 502-5.
6. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; **41**: 145-51.
7. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020; **395**: 809-15.
8. Zhu L, Wang J, Huang R, et al. Clinical characteristics of a case series of children with coronavirus disease 2019. *Pediatr Pulmonol* 2020. DOI: 10.1002/ppul.24767.
9. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in children and adolescents: A systematic review. *JAMA Pediatr 2020.* DOI:10.1001/jamapediatrics.2020.1467.
10. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med* 2020; **382**: 1663-5.
11. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020; DOI: 10.1542/peds.2020-0702.

12. Liu W, Zhang Q, Chen J, et al. Detection of Covid-19 in children in early January 2020 in Wuhan, China. *N Engl J Med* 2020; **382**: 1370-1.
13. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2006100.
14. CDC COVID-19 Response Team. Coronavirus disease 2019 in children - United States, February 12 - April 2, 2020. *MMWR Morb Mortal Wkly* Rep 2020; **69**: 422-6.
15. Basu Roy R, Thee S, Blazquez-Gamero D, et al. Performance of immune-based and microbiological tests in children with TB meningitis in Europe - a multi-center Paediatric Tuberculosis Network European Trials Group (ptbnet) study. *Eur Respir J* 2020; pii: 1902004.
16. Noguera-Julian A, Calzada-Hernandez J, Brinkmann F, et al. Tuberculosis disease in children and adolescents on therapy with anti-tumor necrosis factor-alpha agents: a collaborative, multi-centre ptbnet study. *Clin Infect Dis* 2019; pii: ciz1138.
17. Villanueva P, Neth O, Ritz N, Tebruegge M, Paediatric Tuberculosis Network European Trials Group. Use of Xpert MTB/RIF Ultra assays among paediatric tuberculosis experts in Europe. *Eur Respir J* 2018;5: pii:1800346.
18. Tebruegge M, Ritz N, Koetz K, et al. Availability and use of molecular microbiological and immunological tests for the diagnosis of tuberculosis in Europe. *PLoS One* 2014; **9**: e99129.
19. Tebruegge M, Buonsenso D, Brinkmann F, et al. European shortage of purified protein derivative and its impact on tuberculosis screening practices. *Int J Tuberc Lung Dis* 2016; **20**: 1293-9.
20. Tebruegge M, Bogyi M, Soriano-Arandes A, Kampmann B, Paediatric Tuberculosis Network European Trials Group. Shortage of purified protein derivative for tuberculosis testing. *Lancet* 2014; **384**: 2026.
21. Malaguarnera L, Ferlito L, Imbesi RM, et al. Immunosenescence: a review. *Arch Gerontol Geriatr* 2001; **32**: 1-14.
22. Kollmann TR, Kampmann B, Mazmanian SK, Marchant A, Levy O. Protecting the newborn and young infant from infectious diseases: lessons from immune ontogeny. *Immunity* 2017; **46**: 350-63.
23. Kollmann TR, Crabtree J, Rein-Weston A, et al. Neonatal innate TLR-mediated responses are distinct from those of adults. J *Immunol* 2009; **183**: 7150-60.

24. COVID-19 National Incident Room Surveillance Team. COVID-19, Australia: Epidemiology Report 11 (Reporting week 12 April 2020). *Commun Dis Intell* 2020;44.
25. Parri N, Lenge M, Buonsenso D. Children with COVID-19 in Pediatric emergency departments in Italy. *N Engl J Med 2020*. DOI: 10.1056/NEJMc2007617.
26. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; **395**:1607-8.
27. European Centre for Disease Prevention and Control. Rapid risk assessment: Paediatric inflammatory multisystem syndrome and SARS -CoV-2 infection in children. Available at: https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment. Accessed 25 May 2020.
28. Tagarro A, Epalza C, Santos M, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. *JAMA Pediatr* 2020. DOI:10.1001/jamapediatrics.2020.1346
29. McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. *J Pediatr* 2010; **156**: 634-8.
30. von der Beck D, Seeger W, Herold S, Gunther A, Loh B. Characteristics and outcomes of a cohort hospitalized for pandemic and seasonal influenza in Germany based on nationwide inpatient data. *PLoS One* 2017; **12**: e0180920.
31. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Ped Infect Dis Soc* 2020. DOI: 10.1093/jpids/piaa045.
32. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med 2020*. DOI: 10.1056/NEJMoa2007016.
33. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020; **19**: 149-50.
34. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-Ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2001282.